PCT

RAW SEQUENCE LISTING DATE: 12/10/2004
PATENT APPLICATION: **US/10/516,505** TIME: 14:21:08

Input Set : **A:\PTS-0055WO.txt**
Output Set: **N:\CRF4\12102004\J516505.raw**

3 <110> APPLICANT: ISIS Pharmaceuticals Inc.
4 Eric G. Marcusson
5 C. Frank Bennett
6 Kenneth W. Dobie
8 <120> TITLE OF INVENTION: ANTISENSE MODULATION OF EXTRACELLULAR-SIGNAL-REGULATED KINASE-6 EXPRESSION
10 <130> FILE REFERENCE: PTS-0055WO
C--> 12 **<140> CURRENT APPLICATION NUMBER: US/10/516,505**
C--> 12 **<141> CURRENT FILING DATE: 2004-12-01**
12 <150> PRIOR APPLICATION NUMBER: 10/348,431
13 <151> PRIOR FILING DATE: 2003-01-17
15 <150> PRIOR APPLICATION NUMBER: 10/174,465
16 <151> PRIOR FILING DATE: 2002-06-17
18 <160> NUMBER OF SEQ ID NOS: 233
20 <210> SEQ ID NO: 1
21 <211> LENGTH: 20
22 <212> TYPE: DNA
23 <213> ORGANISM: Artificial Sequence
25 <220> FEATURE:
27 <223> OTHER INFORMATION: Antisense Oligonucleotide
29 <400> SEQUENCE: 1
30 tccgtcatcg ctcctcaggg 20
33 <210> SEQ ID NO: 2
34 <211> LENGTH: 20
35 <212> TYPE: DNA
36 <213> ORGANISM: Artificial Sequence
38 <220> FEATURE:
40 <223> OTHER INFORMATION: Antisense Oligonucleotide
42 <400> SEQUENCE: 2
43 gtgcgcgcga gcccgaaatc 20
46 <210> SEQ ID NO: 3
47 <211> LENGTH: 20
48 <212> TYPE: DNA
49 <213> ORGANISM: Artificial Sequence
51 <220> FEATURE:
53 <223> OTHER INFORMATION: Antisense Oligonucleotide
55 <400> SEQUENCE: 3
56 atgcattctg cccccaagga 20
59 <210> SEQ ID NO: 4
60 <211> LENGTH: 1670
61 <212> TYPE: DNA
62 <213> ORGANISM: H. sapiens
64 <220> FEATURE:
66 <220> FEATURE:

Does Not Comply
Corrected Diskette Needed

p.6

RAW SEQUENCE LISTING DATE: 12/10/2004
PATENT APPLICATION: US/10/516,505 TIME: 14:21:08

Input Set : A:\PTS-0055WO.txt
Output Set: N:\CRF4\12102004\J516505.raw

```
67 <221> NAME/KEY: CDS
68 <222> LOCATION: (34)...(1137)
70 <400> SEQUENCE: 4
71 ggctctgcgg ggtgggcagc tcccgggcct gcc atg agc tct ccg ccg ccc acc     54
72                                    Met Ser Ser Pro Pro Pro Thr
73                                      1               5
75 cgc agt ggc ttt tac cgc cag gag gtg acc aag acg gcc tgg gag gtg     102
76 Arg Ser Gly Phe Tyr Arg Gln Glu Val Thr Lys Thr Ala Trp Glu Val
77          10                  15                  20
79 cgc gcc gtg tac cgg gac ctg cag ccc gtg ggc tcg ggc gcc tac ggc     150
80 Arg Ala Val Tyr Arg Asp Leu Gln Pro Val Gly Ser Gly Ala Tyr Gly
81      25                  30                  35
83 gcg gtg tgc tcg gcc gtg gac ggc cgc acc ggc gct aag gtt gcc atc     198
84 Ala Val Cys Ser Ala Val Asp Gly Arg Thr Gly Ala Lys Val Ala Ile
85  40                  45                  50                  55
87 aag aag ctg tat cgg ccc ttc cag tcc gag ctg ttc gcc aag ctc gcc     246
88 Lys Lys Leu Tyr Arg Pro Phe Gln Ser Glu Leu Phe Ala Lys Leu Ala
89                  60                  65                  70
91 tac cgc gag ctg cgc ctg ctc aag cac atg cgc cac gag aac gtg atc     294
92 Tyr Arg Glu Leu Arg Leu Leu Lys His Met Arg His Glu Asn Val Ile
93              75                  80                  85
95 ggg ctg ctg gac gta ttc act cct gat gag acc ctg gat gac ttc acg     342
96 Gly Leu Leu Asp Val Phe Thr Pro Asp Glu Thr Leu Asp Asp Phe Thr
97          90                  95                  100
99 gac ttt tac ctg gtg atg ccg ttc atg ggc acc gac ctg ggc aag ctc     390
100 Asp Phe Tyr Leu Val Met Pro Phe Met Gly Thr Asp Leu Gly Lys Leu
101     105                 110                 115
103 atg aaa cat gag aag cta ggc gag gac cgg atc cag ttc ctc gtg tac     438
104 Met Lys His Glu Lys Leu Gly Glu Asp Arg Ile Gln Phe Leu Val Tyr
105 120                 125                 130                 135
107 cag atg atg aag ggg ctg agg tat atc cac gct gcc ggc atc atc cac     486
108 Gln Met Met Lys Gly Leu Arg Tyr Ile His Ala Ala Gly Ile Ile His
109                 140                 145                 150
111 aga gac ctg aag ccc ggc aac ctg gct gtg aac gaa gac tgt gag ctg     534
112 Arg Asp Leu Lys Pro Gly Asn Leu Ala Val Asn Glu Asp Cys Glu Leu
113             155                 160                 165
115 aag atc ctg gac ttc ggc ctg gcc agg cag gca gac agt gag atg act     582
116 Lys Ile Leu Asp Phe Gly Leu Ala Arg Gln Ala Asp Ser Glu Met Thr
117         170                 175                 180
119 ggg tac gtg gtg acc cgg tgg tac cgg gct ccc gag gtc atc ttg aat     630
120 Gly Tyr Val Val Thr Arg Trp Tyr Arg Ala Pro Glu Val Ile Leu Asn
121     185                 190                 195
123 tgg atc gcg tac acg cag acg gtg gac atc tgg tct gtg ggc tgc atc     678
124 Trp Ile Ala Tyr Thr Gln Thr Val Asp Ile Trp Ser Val Gly Cys Ile
125 200                 205                 210                 215
127 atg gcg gag atg atc aca ggc aag acg ctg ttc aag ggc agc gac cac     726
128 Met Ala Glu Met Ile Thr Gly Lys Thr Leu Phe Lys Gly Ser Asp His
129                 220                 225                 230
131 ctg gac cag ctg aag gag atc atg aag gtg acg ggg acg cct ccg gct     774
```

RAW SEQUENCE LISTING DATE: 12/10/2004
PATENT APPLICATION: US/10/516,505 TIME: 14:21:08

Input Set : A:\PTS-0055WO.txt
Output Set: N:\CRF4\12102004\J516505.raw

```
132 Leu Asp Gln Leu Lys Glu Ile Met Lys Val Thr Gly Thr Pro Pro Ala
133             235                 240                 245
135 gag ttt gtg cag cgg ctg cag agc gat gag gcc aag aac tac atg aag     822
136 Glu Phe Val Gln Arg Leu Gln Ser Asp Glu Ala Lys Asn Tyr Met Lys
137         250                 255                 260
139 ggc ctc ccc gaa ttg gag aag aag gat ttt gcc tct atc ctg acc aat     870
140 Gly Leu Pro Glu Leu Glu Lys Lys Asp Phe Ala Ser Ile Leu Thr Asn
141     265                 270                 275
143 gca agc cct ctg gct gtg aac ctc ctg gag aag atg ctg gtg ctg gac     918
144 Ala Ser Pro Leu Ala Val Asn Leu Leu Glu Lys Met Leu Val Leu Asp
145 280                 285                 290                 295
147 gcg gac atc agg ttg act gca ggc gag ttt ctt tcc cat ccc tac ttc     966
148 Ala Asp Ile Arg Leu Thr Ala Gly Glu Phe Leu Ser His Pro Tyr Phe
149                 300                 305                 310
151 gag tcc ctg cac gac acg gaa gat gag ccc cag gtc cag aag tat gat    1014
152 Glu Ser Leu His Asp Thr Glu Asp Glu Pro Gln Val Gln Lys Tyr Asp
153             315                 320                 325
155 gac tcc ttt gac tac ttt gac cgc aca ctg gat gaa tgg aag cgt gtt    1062
156 Asp Ser Phe Asp Tyr Phe Asp Arg Thr Leu Asp Glu Trp Lys Arg Val
157         330                 335                 340
159 act tac aaa gag gtg ctc agc ttc aag cct ccc cgg cag ctg ggg gcc    1110
160 Thr Tyr Lys Glu Val Leu Ser Phe Lys Pro Pro Arg Gln Leu Gly Ala
161     345                 350                 355
163 agg gtc tcc aag gag acg cct ctg tga agatctctgg gctccggggt          1157
164 Arg Val Ser Lys Glu Thr Pro Leu
165 360                 365
167 ggcagtgagg accaccttca ccttccacct gagaggggac tctcgttgcc accttgacct  1217
169 tggctggggc ttgcatccca aggcatccat cagagcagac gcccgggttc catggaccct  1277
171 cctccccact gccatgcctc tgctctttgg cgcccatcat ggaggagcac ctgaactttc  1337
173 tggacaagac ctctggccga cctggggatg gcctctgatc cctggagcag tggaacacaa  1397
175 aaaacaatac tctcagaaac ctcagagctg gtggggctcc agatcagcct tggcctctga  1457
177 gccctgcctg ctctgggcca tgcagaggaa ggacagaggg tgggagcagg gcaccaactc  1517
179 agggacatcc cctctcctgg gcgacgtcag tggaccttcc tgcaccccca gcctggaatg  1577
181 taaatcagct gtgtggtgcc cgcgtggctg gaaggaaata gacccttttg tagctccaaa  1637
183 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa                               1670
186 <210> SEQ ID NO: 5
187 <211> LENGTH: 20
188 <212> TYPE: DNA
189 <213> ORGANISM: Artificial Sequence
191 <220> FEATURE:
193 <223> OTHER INFORMATION: PCR Primer
195 <400> SEQUENCE: 5
196 ctcgttgcca ccttgacctt                                               20
199 <210> SEQ ID NO: 6
200 <211> LENGTH: 16
201 <212> TYPE: DNA
202 <213> ORGANISM: Artificial Sequence
204 <220> FEATURE:
206 <223> OTHER INFORMATION: PCR Primer
```

RAW SEQUENCE LISTING DATE: 12/10/2004
PATENT APPLICATION: US/10/516,505 TIME: 14:21:08

Input Set : A:\PTS-0055WO.txt
Output Set: N:\CRF4\12102004\J516505.raw

208 <400> SEQUENCE: 6
209 tggaacccgg gcgtct 16
212 <210> SEQ ID NO: 7
213 <211> LENGTH: 24
214 <212> TYPE: DNA
215 <213> ORGANISM: Artificial Sequence
217 <220> FEATURE:
219 <223> OTHER INFORMATION: PCR Probe
221 <400> SEQUENCE: 7
222 ttgcatccca aggcatccat caga 24
225 <210> SEQ ID NO: 8
226 <211> LENGTH: 19
227 <212> TYPE: DNA
228 <213> ORGANISM: Artificial Sequence
230 <220> FEATURE:
232 <223> OTHER INFORMATION: PCR Primer
234 <400> SEQUENCE: 8
235 gaaggtgaag gtcggagtc 19
238 <210> SEQ ID NO: 9
239 <211> LENGTH: 20
240 <212> TYPE: DNA
241 <213> ORGANISM: Artificial Sequence
243 <220> FEATURE:
245 <223> OTHER INFORMATION: PCR Primer
247 <400> SEQUENCE: 9
248 gaagatggtg atgggatttc 20
251 <210> SEQ ID NO: 10
252 <211> LENGTH: 20
253 <212> TYPE: DNA
254 <213> ORGANISM: Artificial Sequence
256 <220> FEATURE:
258 <223> OTHER INFORMATION: PCR Probe
260 <400> SEQUENCE: 10
261 caagcttccc gttctcagcc 20
264 <210> SEQ ID NO: 11
265 <211> LENGTH: 20
266 <212> TYPE: DNA
267 <213> ORGANISM: Artificial Sequence
269 <220> FEATURE:
271 <223> OTHER INFORMATION: Antisense Oligonucleotide
273 <400> SEQUENCE: 11
274 ccttcatcat ctggtacacg 20
277 <210> SEQ ID NO: 12
278 <211> LENGTH: 20
279 <212> TYPE: DNA
280 <213> ORGANISM: Artificial Sequence
282 <220> FEATURE:
284 <223> OTHER INFORMATION: Antisense Oligonucleotide
286 <400> SEQUENCE: 12

RAW SEQUENCE LISTING DATE: 12/10/2004
PATENT APPLICATION: US/10/516,505 TIME: 14:21:08

Input Set : A:\PTS-0055WO.txt
Output Set: N:\CRF4\12102004\J516505.raw

287 tccttcagct ggtccaggtg 20
290 <210> SEQ ID NO: 13
291 <211> LENGTH: 20
292 <212> TYPE: DNA
293 <213> ORGANISM: Artificial Sequence
295 <220> FEATURE:
297 <223> OTHER INFORMATION: Antisense Oligonucleotide
299 <400> SEQUENCE: 13
300 ccaccagctc tgaggtttct 20
303 <210> SEQ ID NO: 14
304 <211> LENGTH: 20
305 <212> TYPE: DNA
306 <213> ORGANISM: Artificial Sequence
308 <220> FEATURE:
310 <223> OTHER INFORMATION: Antisense Oligonucleotide
312 <400> SEQUENCE: 14
313 ggagagctca tggcaggccc 20
316 <210> SEQ ID NO: 15
317 <211> LENGTH: 20
318 <212> TYPE: DNA
319 <213> ORGANISM: Artificial Sequence
321 <220> FEATURE:
323 <223> OTHER INFORMATION: Antisense Oligonucleotide
325 <400> SEQUENCE: 15
326 gtggcgcatg tgcttgagca 20
329 <210> SEQ ID NO: 16
330 <211> LENGTH: 20
331 <212> TYPE: DNA
332 <213> ORGANISM: Artificial Sequence
334 <220> FEATURE:
336 <223> OTHER INFORMATION: Antisense Oligonucleotide
338 <400> SEQUENCE: 16
339 cccttcatca tctggtacac 20
342 <210> SEQ ID NO: 17
343 <211> LENGTH: 20
344 <212> TYPE: DNA
345 <213> ORGANISM: Artificial Sequence
347 <220> FEATURE:
349 <223> OTHER INFORMATION: Antisense Oligonucleotide
351 <400> SEQUENCE: 17
352 atccagggtc tcatcaggag 20
355 <210> SEQ ID NO: 18
356 <211> LENGTH: 20
357 <212> TYPE: DNA
358 <213> ORGANISM: Artificial Sequence
360 <220> FEATURE:
362 <223> OTHER INFORMATION: Antisense Oligonucleotide
364 <400> SEQUENCE: 18
365 cccggagccc agagatcttc 20

??
??
??
??

delete at end of file

RAW SEQUENCE LISTING ERROR SUMMARY DATE: 12/10/2004
PATENT APPLICATION: **US/10/516,505** TIME: 14:21:09

Input Set : **A:\PTS-0055WO.txt**
Output Set: **N:\CRF4\12102004\J516505.raw**

Please Note:
Use of n and/or Xaa have been detected in the Sequence Listing. Please review the Sequence Listing to ensure that a corresponding explanation is presented in the <220> to <223> fields of each sequence which presents at least one n or Xaa.

Seq#:71; N Pos. 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20
Seq#:75; N Pos. 727

Invalid Line Length:
The rules require that a line not exceed 72 characters in length. This includes spaces.

Seq#:1; Line(s) 8

VERIFICATION SUMMARY DATE: 12/10/2004
PATENT APPLICATION: **US/10/516,505** TIME: 14:21:09

Input Set : **A:\PTS-0055WO.txt**
Output Set: **N:\CRF4\12102004\J516505.raw**

L:12 M:270 C: Current Application Number differs, Replaced Current Application No
L:12 M:271 C: Current Filing Date differs, Replaced Current Filing Date
L:1007 M:281 W: Numeric Fields not Ordered, <221> Sort in ascending order!
L:1011 M:258 W: Mandatory Feature missing, <220> Tag not found for SEQ ID#:71
L:1012 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:71 after pos.:0
L:1307 M:258 W: Mandatory Feature missing, <223> Blank for SEQ#:75,Line#:1305
L:1332 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:75 after pos.:720
L:3333 M:334 W: (2) Invalid Amino Acid in Coding Region, NUMBER OF INVALID KEYS:1
L:3335 M:336 W: Invalid Amino Acid Number in Coding Region, SEQ ID:233
L:3335 M:334 W: (2) Invalid Amino Acid in Coding Region, NUMBER OF INVALID KEYS:1
L:3337 M:336 W: Invalid Amino Acid Number in Coding Region, SEQ ID:233
L:3337 M:334 W: (2) Invalid Amino Acid in Coding Region, NUMBER OF INVALID KEYS:1
L:3339 M:336 W: Invalid Amino Acid Number in Coding Region, SEQ ID:233
L:3339 M:334 W: (2) Invalid Amino Acid in Coding Region, NUMBER OF INVALID KEYS:1